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- (71) Applicant (for all designated States except US): SHASUN CHEMICALS AND DRUGS LIMITED [IN/IN]; Shasun House, 3, Doraiswamy Road, T. Nagar, Chennai 600 017 (IN).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): VITTAL, Tangirala, Venkata, Subramanya, Krishna [IN/IN]; c/o Shasun Chemicals And Drugs Limited, Shasun House, 3, Doraiswamy Road, T. Nagar, Chennai 600 017 (IN). TAJ, Shabbir, Ali [IN/IN]; c/o Shasun Chemicals And Drugs Limited, Shasun House, 3, Doraiswamy Road, T. Nagar, Chennai 600 017 (IN). KODIMUTHALI, Armugam [IN/IN]; c/o Shasun Chemicals And Drugs Limited, Shasun House, 3, Doraiswamy Road, T. Nagar, Chennai 600 017 (IN). MADDALI, Kasturaiah [IN/IN]; c/o Shasun Chemicals And Drugs Limited, Shasun House, 3, Doraiswamy Road, T. Nagar, Chennai 600 017 (IN).
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(54) Title: PREPARATION OF NEW MINERAL ACID ADDITION SALTS OF GABAPENTIN

(57) Abstract: This invention relates to the process of preparing new mineral acid addition salts of Gabapentin and the novel conversion of the acid addition salts of Gabapentin to anhydrous Gabapentin From II directly.

WO 03/070683 A1

TITLE OF THE INVENTION

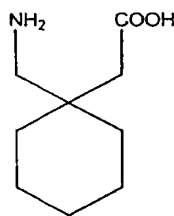
'Preparation Of New Mineral Acid Addition Salts Of Gabapentin.'

FIELD OF THE INVENTION

The present invention relates to a process for preparing mineral acid
5 addition salts of Gabapentin. This invention also relates to a process for
converting mineral acid addition salts of Gabapentin to anhydrous Gabapentin
form II directly.

BACKGROUND OF THE INVENTION

10 Gabapentin is 1-(amino methyl)-1-cyclohexane acetic acid having the
chemical structure is a known drug which was described first time by Warner-
Lambert Co. in US patent no. 4,024,175 in 1977 (The Merck Index. 12th
edition, 1996)



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Gabapentin is used in the treatment of cerebral diseases such as
epilepsy, hypokinesia, cranial trachmas and the like. Gabapentin
(Neurontin.RTM.) is a structural analogue of .gamma.-aminobutyric acid
20 (GABA), the major inhibitory neurotransmitter in mammalian brain.
However, unlike GABA, it readily penetrates the blood-brain barrier and it
does not interact with either GABA.sub.A or GABA.sub.B receptors.

The literature describes various methods of preparing Gabapentin in
different approaches with a variety of starting materials. U.S. Patent No.
25 4,024,175 described at least three methods of preparing Gabapentin from

Cyclohexane diacetic acid mono amide through, Hoffmann, Curtius and the Lossen rearrangements. The product that is isolated in these methods is Gabapentin HCl salt, which on treatment with base ion exchanger liberates the free Gabapentin.

5 U.S. Patent No. 4,894,476 specially discloses an improved method of converting Gabapentin HCl to the Gabapentin. This method involves the treatment of aqueous solution of Gabapentin HCl with base ion exchange resin to afford Gabapentin monohydrate, which on further treatment with methanol and isopropyl alcohol mixture affords the anhydrous Gabapentin.

10 U.S. Patent No. 6,255,526 B1 discloses the preparation of Gabapentin HCl which is substantially free from the inorganic salts and the treatment of the pure Gabapentin HCl with bases like triethyl amine, tributyl amine in a solvent in which the hydrochloride of the corresponding bases are soluble but the Gabapentin is insoluble. This process liberates the crystalline polymorph of Gabapentin form III
15 and the conversion of Gabapentin form III to form II is accomplished by the literature methods known in the art.

Alternate methods of preparing pure Gabapentin, which avoids the formation of HCl, salt or any other mineral acid salts are also available in the literature. U.S. pat. Nos. 5,132,451, U.S. 5,095,148 E, U.S. 5,068,413
20 discloses the methods comprising the formation of cyanic acid derivatives, which are then hydrogenated under drastic conditions to generate Gabapentin.

U.S. Patent No. 5,091,567 offers different method for the preparation of Gabapentin starting from cyclohexanone in three steps to produce Gabapentin lactam. The lactam on hydrolysis in the presence of dilute HCl affords the
25 Gabapentin HCl, which on further treatment with base ion exchange resin affords the pure Gabapentin. These patents are incorporated by reference.

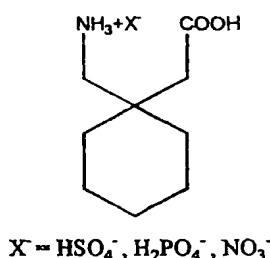
SUMMARY OF THE INVENTION

The object of the present invention to provide a process for the preparation of new mineral acid addition salts of Gabapentin starting from cyclohexane diacetic acid monoamide, which are substantially free from the
 5 Gabapentin lactam.

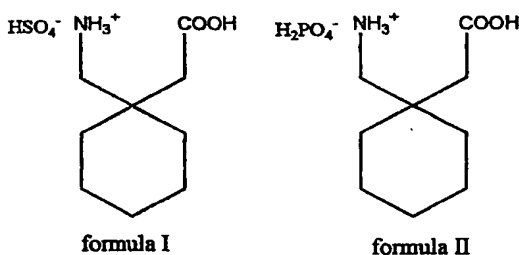
The novel mineral acid addition salt of Gabapentin are useful intermediates for the synthesis of anhydrous Gabapentin form II

To achieve the said objective the present invention relates a novel mineral acid addition salt of Gabapentin of general formula

10



In particular, the novel mineral acid addition salt of Gabapentin is Gabapentin hydrogen sulphate of formula I and Gabapentin dihydrogen
 15 phosphate of formula II.



This invention also relates to a process for preparing mineral acid addition salts of Gabapentin comprising:-

- 20 (a) treating cyclohexane diacetic acid monoamide with sodium hypobromite;

- (b) acidifying said reaction mass with mineral acid to a pH of about 2;
- (c) extracting the acid addition salt with hydrocarbon solvents containing carbonyl group;
- 5 (d) evaporating the said solvent;
- (e) dissolving the extract in alcohol solvent;
- (f) filtering the undissolved material and evaporating the alcohol solvent to obtain a syrupy residue and
- (g) mixing the said residue with non- polar organic solvents to
- 10 obtain mineral acid addition salts of Gabapentin.

In step (a) cyclohexane diacetic acid monoamide is reacted with sodium hypobromite at a temperature between about -10°C to 0°C , warmed to 60°C and thereafter cooled to ambient temperature immediately.

15 The reaction mass is cooled to $15-20^{\circ}\text{C}$. The mineral acid includes concentrated sulfuric acid, phosphoric acid and nitric acid.

The said aliphatic hydrocarbon solvent containing carbonyl group is preferably a keto group having a specific gravity less than that of water and includes acetone, methyl ethyl ketone, methyl isopropyl ketone, methyl

20 isobutyl ketone preferably methyl ethyl ketone.

Step (d) comprises evaporating the said solvent under reduced pressure at temperature between about 30°C - 60°C , preferably between 40°C - 50°C , most preferably 40°C .

The said alcohol solvent includes primary, secondary and tertiary

25 alcohol and is selected from methanol, ethanol, n-propanol, n-butanol, isopropyl alcohol, secondary butyl alcohol, tertiary butyl alcohol, preferably from methanol, isopropyl alcohol or ethanol, and most preferably from isopropyl alcohol.

The said non-polar organic solvent is selected from low boiling aromatic hydrocarbon, halogenated solvents and lower alkyl esters of acetic acid. The said low boiling aromatic hydrocarbon includes benzene and toluene preferably toluene. The said halogenated solvents includes
5 dichloromethane, chloroform, ethylene dichloride, trichloro ethylene. The said lower alkyl ester includes methyl acetate or ethyl acetate.

The said mineral acid addition salt of Gabapentin is converted to anhydrous Gabapentin form II by neutralization reaction. Said neutralization reaction comprises:

- 10 (a) dissolving said acid addition salt of Gabapentin in alcohol solvent and
- (b) neutralizing the salt with organic bases to obtain anhydrous Gabapentin form II.

The neutralization reaction is carried out at a temperature between 10
15 °C - 60 °C for about 6- 48 hours preferably 25 –30 °C for 12-24 hours. Said alcohol solvent are polar protic solvents such as primary, secondary or tertiary alcohol or mixtures thereof. Said alcohol solvent includes methanol, ethanol, isopropanol, n-propanol, n-butanol and t-butanol or mixtures thereof, preferably a mixture of isopropanol and methanol. The ratio in which
20 isopropanol is diluted with methanol is 1:1 to 4:1 by volume preferably 1:1 to 2:1.

The said organic base is an amine. Said amines include trimethylamine, triethylamine, tributylamine, tripropylamine, trihexylamine, preferably triethyl amine.

25

DETAILED DESCRIPTION OF THE INVENTION

Cyclohexane diacetic acid monoamide is treated with sodium hypobromite solution at –10°C to 0°C and is allowed to warm to 60°C. The reaction mass is cooled immediately without further maintenance to ambient

temperature preferably at 15-20°C. In this way the Gabapentin lactam formation is suppressed quantitatively. The reaction mass is acidified with mineral acids to pH 2. The mineral acids include the concentrated Sulphuric acid; Phosphoric acid, HNO_3 , H_2PO_3 etc., The acid addition salt that is present
5 in the aqueous layer is extracted with aliphatic hydrocarbon solvents containing the carbonyl group preferably the keto group wherein the specific gravity of the solvents is less than water. The solvents include acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl isopropyl ketone etc., The solvent after the extraction from the aqueous layer is evaporated under
10 reduced pressure at temperatures in the range of 30°C-60°C preferably at 40°C -50°C to complete dryness. The crude product thus obtained was redissolved in an alcohol solvent wherein the mineral acid addition salts are highly soluble, for example the primary, secondary, tertiary alcohols that includes methanol, ethanol, n-propanol, n-butanol, isopropyl alcohol,
15 secondary butyl alcohol, tertiary butyl alcohol etc.; The preferred solvents include methanol, ethanol or isopropyl alcohol. The solution is maintained at -5°C to 40°C preferably at 10°C-20°C and the undissolved material is filtered completely. The alcohol mother liquor that is obtained after the filtration is evaporated under reduced pressure to dryness at temperatures from 30°C to
20 70°C preferably at 35°C-40°C to afford a syrupy residue. The residue is slurried to get the product in non polar organic solvents preferably the low boiling aromatic hydrocarbon, halogenated solvents and the lower alkyl esters of acetic acid. The low boiling aromatic hydrocarbons include benzene, toluene etc., and the halogenated solvents include dichloromethane,
25 chloroform, ethylene dichloride, trichloro ethylene etc. The lower alkyl esters of acetic acid includes methyl acetate, ethyl acetate etc.,

The acid addition salt that is obtained is substantially free from all the inorganic salts and can be taken up for the neutralisation to liberate the anhydrous Gabapentin Form II.

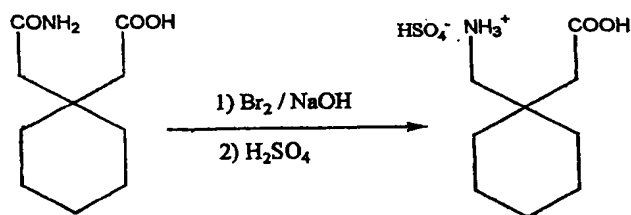
The neutralisation of acid addition salt of Gabapentin can be accomplished by neutralising the salt with organic bases particularly the amines. The amines include trimethylamine, triethylamine, tributylamine, tripropylamine, trihexylamine etc., The preferred solvents for neutralisation are polar protic solvents preferably the alcohol solvents for example the primary, secondary, tertiary alcohol wherein the mineral acid addition salts of the Gabapentin are freely soluble at ambient temperatures. The neutralisation is accomplished with mixture of alcohol solvents wherein the Gabapentin Form II is liberated directly from the reaction. The mixture of alcohol solvents that are used for neutralisation in which the acid addition salts are freely soluble includes methanol, ethanol, isopropanol, n-propanol, n-butanol and t-butanol etc.,

Thus the acid addition salt of Gabapentin is dissolved in an alcohol solvent, for example in isopropanol, n-propanol, n-butanol, isobutanol, t-butanol etc., Preferably in isopropanol and is diluted with methanol. The dilution ratio of isopropanol to methanol that used for the reaction varies from 1:1 to 4:1 by volume preferably in the range of 1:1 to 2:1 and the temperature of the reaction varies from 10°C-60°C. Preferably in the range of 25°C-30°C. The time that is required for the complete conversion of Gabapentin acid addition salt to Gabapentin form II is around 6-48 hours preferably the time required is 12-24 hours. The product that is precipitated from the reaction mass is filtered, dried and the dried product is pure enough which does not require any further purification. The product meets all the specification of Anhydrous Gabapentin Form II.

The present invention will now be explained with reference to the foregoing examples.

Example 1

Preparation of Gabapentin Hydrogen Sulphate:



Sodium hydroxide (301 gm, 7.542 mol), water (1.2 lit) are charged into 3 litre flask and the solution is cooled to -5°C , Bromine (80 ml, 1.553 mol) is added very slowly over period of 30 minutes at below 0°C under stirring. The reaction was maintained at below 0°C for another 30 minutes. Cyclohexane diacetic acid monoamide (250 gm, 1.256 mol) was added portion wise below 0°C over a period of 30 minutes. The reaction mixture is warmed to 60°C and is again cooled to below 20°C . The reaction mass is acidified with Conc. H_2SO_4 (170 ml) to pH 2 and the reaction mass is diluted with methyl ethyl ketone (600 ml). The organic layer is separated and the aqueous layer is again extracted with methyl ethyl ketone (2x300 ml). The combined organic layers are concentrated under reduced pressure at 40°C to the complete dryness. The thick syrupy residue that is obtained is diluted with isopropyl alcohol (1l) and the solution is cooled to 10°C under stirring. The undissolved material is filtered over celite and concentrated under reduced pressure at below 30°C . The syrupy residue is slurried in ethyl acetate, filtered, and dried, to afford Gabapentin hydrogen sulphate in 80% yield.

M.P. $141 - 142^{\circ}\text{C}$.

^1H NMR ($\text{DMSO}-d_6$, 300 MHZ) δ : 1.39 -1.42 (brd, 10 H), 2.38 (S, 2H), 2.93 (S, 2H), 7.74 (brs, D_2O exchangeable), 12.41 (brs, D_2O exchangeable)

^{13}C NMR ($\text{DMSO}-d_6$, 300 MHZ) δ : 20.612, 25.220, 32.436, 34.577, 45.206, and 172.929.

IR (KBr) cm^{-1} : 3390.2, 3056.1, 2932.7, 1713.5, 1624.0, 1579.0, 1519.9, 1388.1, 1198.6, 852.3, 682.6, and 502.0.

C, H, N analysis:

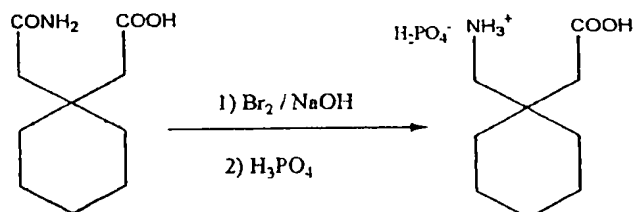
Calculated: C: 40.15%, H: 7.43%, N: 5.20%

Found: C: 40.32%, H: 7.38%, N: 5.12%

Example 2

Preparation of Gabapentin dihydrogen phosphate salt.

5



Sodium hydroxide (301 gm, 7.542 mol), water (1.2 lit) are charged into 3 litre flask and the solution is cooled to -5°C , bromine (80 ml, 1.553 mol) is added very slowly over period of 30 minutes at below 0°C under stirring. The reaction was maintained at below 0°C for another 30 minutes. Cyclohexane diacetic acid monoamide (250 gm, 1.256 mol) was added portion wise below 0°C over a period of 30 minutes. The reaction mixture is warmed to 60°C and is again cooled to below 20°C . The reaction mass is acidified with Phosphoric acid (300 ml) to pH 2 and the reaction mass is diluted with methyl ethyl ketone (600 ml). The organic layer is separated and the aqueous layer is again extracted with methyl ethyl ketone (2x300 ml). The combined organic layers are concentrated under reduced pressure at 40°C to the complete dryness. The thick syrupy residue obtained is diluted with isopropyl alcohol (1l) and the solution is cooled to 10°C under stirring. The undissolved material is filtered over celite and concentrated under reduced pressure at below 30°C . The syrupy residue is slurried in toluene, filtered, and dried to afford Gabapentin dihydrogen phosphate in 90% yield.

^1H NMR (DMSO- d_6 300 MHZ) δ : 1.42 (brs, 10 H), 2.38 (s, 2H) 2.91 (s, 2H), 3.5 (brs, D_2O exchangeable) 7.83 (brs, D_2O exchangeable).

^{13}C NMR (DMSO- d_6 , 300 MHz) δ : 20.787, 25.313, 32.568, 34.678, 47.363, 173.059.

IR (KBr) cm^{-1} : 3418.8, 2936.7, 2387.9, 1690.3, 1508.2, 1182.4, 1140.7, 1075.4, 1006.3, 922.0, and 533.0

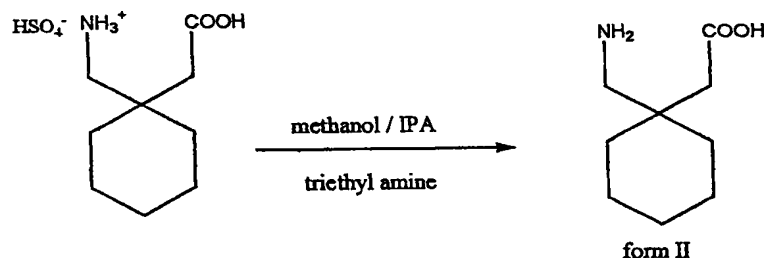
5 C, H, N analysis:

Calculated: C: 40.15%, H: 7.50%, N: 5.20%

Found: C: 40.32%, H: 7.42%, N: 4.98%

Example 3

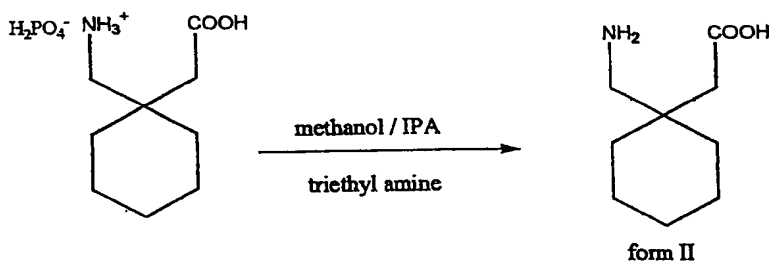
10 Preparation of Gabapentin



Gabapentin Hydrogen Sulphate (250 g) was dissolved in 1 litre of Isopropyl alcohol in 3 litre flask and is diluted with methanol (500ml) at room temperature Tri ethyl amine (135.4 ml) was added very slowly at room temperature and the reaction mixture was maintained at room temperature for 24 hours. The precipitated product is filtered, dried to afford Gabapentin form II in 80% yield.

Example 4

20 Preparation of Gabapentin

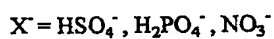
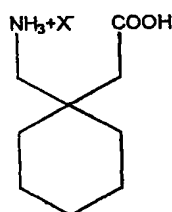


Gabapentin dihydrogen phosphate (250 g) was dissolved in 1 litre of Isopropyl alcohol in 3 litre flask and is diluted with methanol (500ml) at room temperature. Tri ethyl amine (135.4 ml) was added very slowly at room temperature and the reaction mixture was maintained at room temperature for 24 hours. The precipitated product is filtered, dried to afford Gabapentin form II in 60% yield.

While the present invention has been particularly shown and described with reference to the examples thereof, it will be understood by those skilled in the art that various changes in form and details may be effected therein without departing from the spirit and scope of the invention as defined by the appended claims.

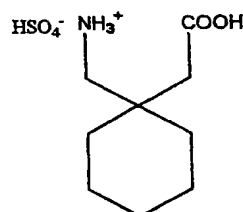
CLAIMS:

1. A novel mineral acid addition salt of Gabapentin of the general formula



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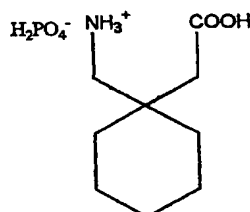
2. A novel mineral acid addition salt of Gabapentin as claimed in claim 1 wherein said salt is Gabapentin hydrogen sulphate of formula I.



formula I

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3. A novel mineral acid addition salt of Gabapentin as claimed in claim 1 wherein said salt is Gabapentin dihydrogen phosphate of formula II.



formula II

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4. A process for preparing mineral acid addition salts of Gabapentin as claimed in claim 1 comprising:-

- (a) treating cyclohexane diacetic acid monoamide with sodium hypobromite;
- (b) acidifying said reaction mass with mineral acid to a pH of about 2;
- 5 (c) extracting the acid addition salt with hydrocarbon solvents containing carbonyl group;
- (d) evaporating the said solvent;
- (e) dissolving the extract in alcohol solvent;
- (f) filtering the undissolved material and evaporating the alcohol solvent to obtain a syrupy residue and
- 10 (g) mixing the said residue with non- polar organic solvents to obtain mineral acid addition salts of Gabapentin.

5. A process as claimed in claim 4 wherein in step (a) cyclohexane diacetic acid monoamide is reacted with sodium hypobromite at a temperature between about -10°C to 0°C , warmed to 60°C and thereafter cooled to ambient temperature immediately.

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6. A process as claimed in claim 4 wherein the reaction mass is cooled to $15-20^{\circ}\text{C}$

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7. A process as claimed in claim 4 wherein said mineral acid includes concentrated sulfuric acid, phosphoric acid, and nitric acid.

8. A process as claimed in claim 4 wherein said aliphatic hydrocarbon solvent containing carbonyl group is preferably a keto group having a specific gravity less than that of water.

25

9. A process as claimed in claim 4 wherein said solvent includes acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone
10. A process as claimed in claim 9 wherein said solvent is methyl ethyl ketone.
11. A process as claimed in claim 4 wherein step (d) comprises evaporating the said solvent under reduced pressure at temperature between about 30°-60°C.
12. A process as claimed in claim 11 said solvent is evaporated under reduced pressure at temperature between 40°-50°C, preferably 40°C.
13. A process as claimed in claim 4 wherein said alcohol solvent includes primary, secondary and tertiary alcohol.
14. A process as claimed in claim 13 wherein said alcohol is selected from methanol, ethanol, n-propanol, n-butanol, isopropyl alcohol, secondary butyl alcohol, and tertiary butyl alcohol.
15. A process as claimed in claim 14 wherein said alcohol is selected from methanol, isopropyl alcohol or ethanol, preferably isopropyl alcohol.
16. A process as claimed in claim 4 wherein said non-polar organic solvent is selected from low boiling aromatic hydrocarbon, halogenated solvents and lower alkyl esters of acetic acid.
17. A process as claimed in claim 16 wherein said low boiling aromatic hydrocarbon includes benzene and toluene, preferably toluene.

18. A process as claimed in claim 16 wherein said halogenated solvents includes dichloromethane, chloroform, ethylene dichloride, trichloro ethylene.
- 5 19. A process as claimed in claim 16 wherein said lower alkyl ester includes methyl acetate or ethyl acetate.
20. A process as claimed in claim 4 wherein said mineral acid addition salt of Gabapentin is converted to anhydrous Gabapentin form II by neutralization
10 reaction.
21. A process as claimed in claim 20 wherein said neutralization reaction comprises:
- (a) dissolving said acid addition salt of Gabapentin in alcohol
15 solvent and
 - (b) neutralizing the salt with organic bases to obtain anhydrous Gabapentin form II.
22. A process as claimed in claim 20 wherein the neutralization reaction is
20 carried out at a temperature between 10 °C - 60 °C for about 6- 48 hours preferably 25 -30 °C for 12-24 hours.
23. A process as claimed in claim 21 wherein said alcohol solvent are polar protic solvents.
- 25 24. A process as claimed in claim 21 wherein said protic solvent includes primary, secondary or tertiary alcohol or mixtures thereof.

25. A process as claimed in claim 24 wherein said alcohol includes methanol, ethanol, isopropanol, n-propanol, n-butanol and t-butanol or mixtures thereof, preferably a mixture of isopropanol and methanol.

5 26. A process as claimed in claim 25 wherein said the ratio in which isopropanol is diluted with methanol is 1:1 to 4:1 by volume preferably 1:1 to 2:1.(please check this ratio)

27. A process as claimed in claim 21 wherein said organic base is an amine

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28. A process as claimed in claim 27 wherein said amines include trimethylamine, triethylamine, tributylamine, tripropylamine, trihexylamine, preferably triethylamine

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/90192

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 61/06

US CL : 562/507

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 562/507

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,319,135 A (JENNINGS et al) 07 June 1994 (07.06.1994), see entire document.	1-28
A	US 6,255,526 B1 (PESACHOVICH et al.) 03 July 2001 (03.07.2001), see entire document.	1-28

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

08 July 2002 (08.07.2002)

Date of mailing of the international search report

01 OCT 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Johann Richter

Telephone No. 703-308-1123